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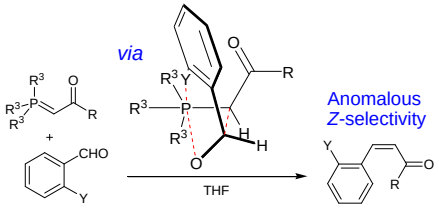

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Anomalous *Z*-selectivity in Wittig reactions of keto-stabilised ylides with *ortho*-heteroatom substituted benzaldehydes

Peter A. Byrne,[a] Lee J. Higham,[b] Pádraic McGovern[a] and Declan G. Gilheany[a]*

[a]*Centre for Synthesis & Chemical Biology, Conway Institute of Biomolecular and Biomedical Research, School of Chemistry and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland.*
[b]*School of Chemistry, Bedson Building, Newcastle University, Newcastle upon Tyne, NE1 7RU, UK.*

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ABSTRACT

Wittig reactions of keto-stabilised ylides with *ortho*-substituted benzaldehydes are found to show significantly higher *Z*-selectivity than analogous reactions of the same ylides with benzaldehyde itself. A cooperative effect is seen whereby the unusual *Z*-selectivity is further augmented if the ylide bears greater steric bulk in the α'-position. These results are consistent with our previous observations on reactions of all ylide types with aldehydes bearing a β-heteroatom. Significantly, the cooperative effect, previously limited to semi-stabilised ylides, has now been extended to stabilised ylides. Both the anomalous *Z*-selectivity and the cooperative effect can be rationalised within the [2+2] cycloaddition mechanism of the Wittig reaction.

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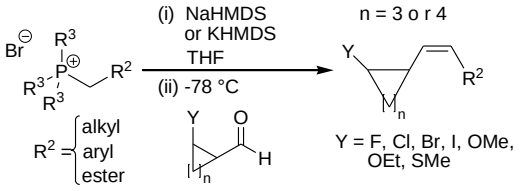
1. Introduction

The Wittig reaction[1] is perhaps the most commonly used method for the synthesis of alkenes. The many and varied applications of it and the extensive work that has been done on its mechanism can be found in various excellent reviews.[2-6] A list of the very latest developments in the Wittig reaction can be found in our recent publication on the mechanism.[7] In the latter work, we believe that we have definitively shown the unity of the mechanism of the Li-salt free Wittig reaction.[7] By this we mean that all ylide types (unstabilised, semi-stabilised and stabilized) react by the same mechanism. Our conclusions were based on the results of Wittig reactions of β-heteroatom substituted aldehydes, which showed unexpectedly high selectivity for *Z*-alkene for all ylide types (see Scheme 1). Such selectivity is not seen in reactions of the same ylides with analogous aldehydes lacking the suitably placed β-heteroatom.

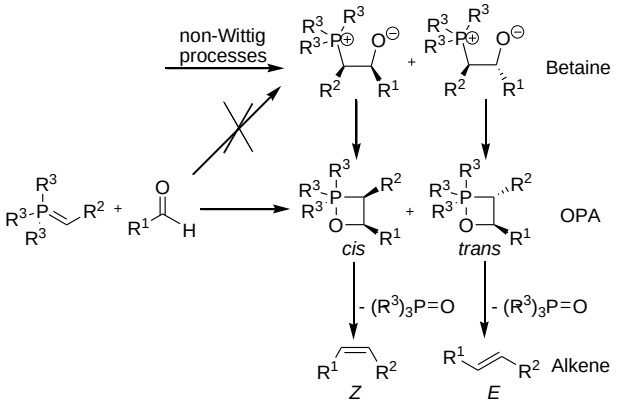
We showed that this change of selectivity, which was rather dramatic in many cases, could be easily accommodated within the emerging consensus[4,8-18] on the mechanism of Li-salt free Wittig reaction: [2+2] cycloaddition of ylide and aldehyde to give oxaphosphetane (OPA) followed by cycloreversion to phosphine oxide and alkene (see Scheme 2). Therefore our results also provided strong experimental support for that mechanism.[19,20]



Scheme 1. Highly *Z*-selective Wittig reactions of β-heteroatom-substituted aldehydes under conditions promoting kinetic control.

Our explanation for the heteroatom-induced increase in *Z*-selectivity involved an additional bonding interaction in the *cis*-selective cycloaddition transition state (TS), between phosphorus and the β-heteroatom, as shown in Fig. 1(a).[7]

* Declan Gilheany. Tel.: +353-1-716-2308; e-mail: declan.gilheany@ucd.ie



Scheme 2. [2+2] cycloaddition mechanism for the Li salt-free Wittig reaction.

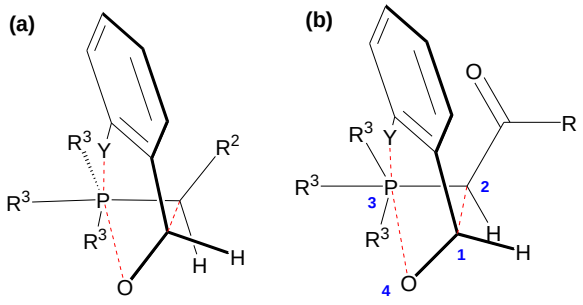
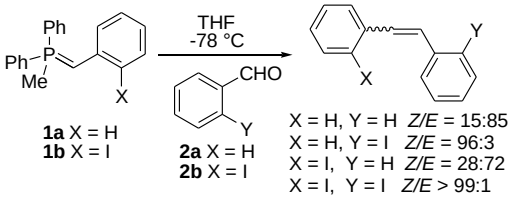


Figure 1. (a) Favoured *cis*-selective TS in reactions of β-heteroatom substituted aldehydes (e.g. *ortho*-substituted benzaldehyde) with non-stabilised (R^2 = alkyl), semi-stabilised (R^2 = aryl), and ester-stabilised (R^2 = CO_2R) ylides; (b) Proposed *cis*-selective TS for similar reactions of keto-stabilised ylides, showing the numbering of the forming ring.

A subsidiary, but important, part of our study concerned an unexpected co-operative effect seen in the case of semi-stabilised ylides. This was also explicable on the proposed TS model, and is illustrated by the data in Scheme 3: the placement of an *ortho*-substituent on the ylide gives an *even greater shift* towards high *Z*-selectivity than the corresponding reaction of the unsubstituted benzylide. For example (Scheme 3), in reaction with *ortho*-iodobenzaldehyde, the *Z*/*E* ratio changes from 96:4 to 99:1 on placement of an iodo-substituent on the benzylide (ylide **1a** vs. **1b**) even though in reaction with benzaldehyde the same change has little effect (15:85 vs. 28:72). This indicates a greater decrease (by *ca.* 1 kJ mol^{-1}) in the energy of the *cis*-selective TS in the reactions of *ortho*-iodo ylide **1b** than in the reactions of unsubstituted benzylide **1a**. According to our TS model, the increased 2-3 interactions (see Fig. 1b for numbering) that would be engendered by the larger aryl group on the ylide α-carbon of *ortho*-substituted benzylides should result in a greater bias towards the *cis*-selective TS, since it is better able to accommodate steric bulk in this position. We refer to this as a "cooperative effect" between the substituents on the ylide and aldehyde which results in a greater shift in *Z*-selectivity than is possible if either of the substituents is not present.

We were interested to see if this cooperative effect could be extended to stabilized ylides. In our previous publication[7] we focused on reactions of various alkyl ester-stabilised ylides. These showed the main effect of increased *Z*-selectivity but there was no analogue of the cooperative effect seen in reactions of benzylides. We attributed this to the larger distance of the variable alkyl group from the ylide α-carbon in these compounds. In seeking a series of stabilised ylides that would be more suitable candidates for the demonstration of the cooperative effect, we turned our attention to Wittig reactions of keto-stabilised ylides, in which sterically bulky groups can be directly attached to the carbonyl group, mimicking the situation in the semi-stabilised cases.



Scheme 3. Wittig reactions of benzaldehydes **2a** and **2b** with benzylides **1a** and **1b** (produced *in situ* by the treatment of the parent phosphonium salts with NaHMDS in THF).

Our objectives then were to determine (i) whether there would be an increase in *Z*-selectivity on substitution of a heteroatom β to the aldehyde, further confirming the generality of the main effect and (ii) whether a cooperative effect (further increase in *Z*-selectivity) would be observed in reactions of keto-stabilised ylides with a more heavily substituted α'-carbon (carbon-3 of the oxoalkylidene moiety). The proposed *cis*-selective TS for these reactions, whose existence we sought to confirm, is analogous to the one proposed previously for reactions of non-stabilised, semi-stabilised, and ester-stabilised ylides with β-heteroatom substituted aldehydes (see Fig. 1(b)).[7] As in the previous study[7] we chose to focus on ylides derived from methyldiphenylphosphine, since kinetic control has previously been established in reactions of such ylides,[7,16] but a small number of triphenylphosphine-derived cases are also included for comparison, as are some ester-stabilised ylides.

We find that there is indeed evidence for a cooperative effect with these ylides, but at a reduced level. The various new substituted enones generated by these studies proved difficult to handle and it was with great difficulty that many of the *Z*/*E* ratios were obtained; some consistently underwent decomposition and, in all cases the *Z*-isomers were extremely prone to isomerisation to the *E*-isomer. Therefore, despite the precautions taken to accurately measure the "kinetic *Z*/*E* ratio" of each reaction,[21] the ratios quoted below represent only a *lower bound* to the true *Z*-selectivity of these reactions.

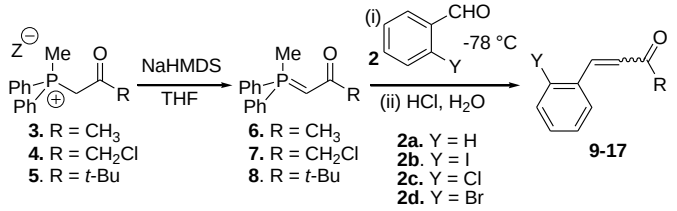
2. Reactions of *ortho*-heteroatom substituted benzaldehydes with keto-stabilised & ester-stabilised ylides

All reactions were carried out using the standard set of reaction conditions established in our previous study,[7] with the exception that, for solubility reasons, certain reactions were carried out at higher temperatures. The ylide was generated *in situ* from the parent phosphonium bromide or chloride salt using non-nucleophilic NaHMDS base in THF (giving insoluble NaCl or NaBr) under an atmosphere of dry nitrogen, and then cooled to -78 °C. The aldehyde was then added dropwise to the cold ylide solution, and the reaction was stirred at low temperature for 20 minutes. Some of the reactions were quenched at low temperature by addition of acid to ensure that the reaction had occurred at that temperature. The *Z*/*E* ratios of the alkenes produced in reactions of 2-oxoalkylidenemethyldiphenylphosphoranes with selected benzaldehydes are shown in Table 1.

Acetonylidenemethyldiphenylphosphorane (**6**, R = CH_3 in the diagram accompanying Table 1) was found to be insoluble in

THF below –50 °C and attempted Wittig reactions with it at temperatures below that (with low temperature quenching) yielded no alkene product. Therefore its reactions were carried out at –45 °C or 20 °C. The reactions of this ylide with benzaldehyde (**2a**) showed high *E*-selectivity (Table 1 entries 1 & 2), while its reactions with *ortho*-heteroatom substituted benzaldehydes (**2c**–**d**) showed a moderate increase in *Z*-selectivity (up to 30 or 40% *Z*-isomer produced, see Table 1 entries 3 & 4). Thus the aldehyde *ortho*-heteroatom-induced increase in *Z*-selectivity previously observed in reactions of non-stabilised, semi-stabilised and ester-stabilised ylides is also observed in reactions of keto-stabilised ylides. The magnitude of the shift in the energy of the *cis*-selective TS is not as great as was generally observed in our previously disclosed results.[7]

Table 1. *Z/E* ratio[a] for reactions of selected 2-oxoalkylidenemethyldiphenylphosphoranes **6-8** (generated *in-situ* from the corresponding phosphonium salts **3-5**)[b] with selected benzaldehydes **2a-d**.[c]



Entry	Ylide R	Aldehyde Y	Temp °C	Enone *Z/E* ratio
1[d]	CH_3	H	-45	19:81
2[e]	CH_3	H	20	20:80
3[d]	CH_3	Cl	-45	33:67
4[e]	CH_3	Br	20	40:60
5[f]	CH_2Cl	H	-78	12:88
6[d,g]	*t*-Bu	H	-78	17:83
7[d]	CH_2Cl	Cl	-78	50:50
8[f]	CH_2Cl	Br	-78	50:50
9[d,g]	*t*-Bu	Br	-78	48:52
10[d,g]	*t*-Bu	I	-78	50:50

[a] *Z/E* ratio determined by ^{1}H NMR analysis of the crude product obtained after aqueous work-up of the reaction mixture. See ESI for full details.

[b] Phosphonium salt counter-ion Z = Cl^- except where otherwise noted.

[c] Ylides (**6**-**8**) were generated at 20 °C from the parent phosphonium salts (**3**-**5**) in dry THF by treatment with NaHMDS. The ylide solution was then brought to the reaction temperature indicated, and the appropriately substituted benzaldehyde was added dropwise. After stirring for 20 minutes, the reaction was quenched as indicated in footnotes *d-f* below.

[d] Quenched with 5% aqueous HCl after 20 minutes at the reaction temperature indicated.

[e] Reactions at 20 °C stirred for 4 h, then quenched with 5% aqueous HCl.

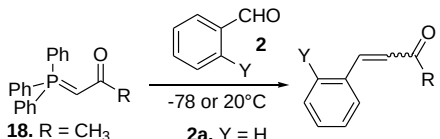
[f] Removed from cooling bath after 20 minutes, and stirred for 12 hours at room temperature before being quenched with 5% aqueous HCl.

[g] Counter-ion Z = Br^-.

Ylides with one or more substituents on carbon-3 of the 2-oxoalkylidene group (**7** and **8**) gave rise to increased *E*-selectivity in their reactions with benzaldehyde (Table 1 entries 5 & 6) but with *ortho*-heteroatom substituted benzaldehydes **2b-d** (Table 1 entries 7-10) they gave considerably increased *Z*-selectivity by comparison, indicating the operation of the same cooperative effect previously observed in reactions of semi-stabilised ylides with benzaldehydes.[7] In summary, the unsubstituted acetonylide (**6**) reacts with benzaldehyde (**2a**) with reasonably high *E*-selectivity, and reacts with *ortho*-heteroatom substituted benzaldehydes (**2c-d**) with somewhat increased *Z*-selectivity. By comparison, the shift in *Z*-selectivity from the more *E*-selective reactions of **7** and **8** (which have greater steric bulk at carbon-3 of the oxoalkylidene moiety) with benzaldehyde to the reactions of the same ylides with *ortho*-heteroatom substituted benzaldehydes **2b-d** is much greater.

The *Z/E* ratios for alkenes produced in reactions of keto-stabilised ylides derived from triphenylphosphine are shown in Table 2. These were carried out using pre-formed ylide (i.e. not generated *in situ*) at -78 °C but not quenched until they had been allowed to warm to room temperature. Thus the actual reaction temperature is not certain for these reactions.

Table 2. *Z/E* ratio[a] for alkenes produced in the reactions of selected acetonylidenetriphenylphosphoranes **18** and **19**,[b] and (*tert*-butoxycarbonylmethylidene)triphenylphosphorane **20**[c] with selected benzaldehydes **2a** and **2d-f**.[d]



Entry	Ylide R	Aldehyde Y	Enone *Z/E* ratio
1	CH_3	H	3:97
2	CH_3	Br	11:89
3	CH_3	OMe	10:90
4	CH_2OMe	Br	17:83
5[c,e]	O(*t*-Bu)	H	3:97
6[c,e]	O(*t*-Bu)	Me	3:97
7[c]	O(*t*-Bu)	Br	20:80
8[c]	O(*t*-Bu)	OMe	19:81

[a] *Z/E* ratio determined by ^{1}H NMR analysis of the crude product obtained after aqueous work-up of the reaction mixture. See ESI for full details.

[b] Pre-formed ylides were used unless otherwise indicated.

[c] Ylide **20** was generated *in situ* from the (commercially available) parent phosphonium salt (*tert*-butoxycarbonylmethyl)triphenylphosphonium chloride. Reactions of this ylide were carried out at 20 °C

[d] Unless otherwise indicated, reactions were stirred at -78 °C for 20 minutes and then allowed to warm to 20 °C.

[e] This result was reported in reference 22.

The reaction of acetonylidenetriphenylphosphorane (**18**) with benzaldehyde (**2a**) yields the expected very high *E*-selectivity in reaction with benzaldehyde (Table 2 entry 1), while its reactions with *ortho*-heteroatom substituted benzaldehydes (**2d-e**) are

somewhat more *Z*-selective (Table 2 entries 2 & 3). The reaction of 3-methoxy-2-oxopropylidenetriphenylphosphorane (**19**) with 2-bromobenzaldehyde (**2d**) shows a further increase in *Z*-selectivity (Table 2 entry 4). Thus the trends observed for the reactions of 2-oxoalkylidenemethyldiphenylphosphoranes detailed in Table 1 are reproduced here – including the operation of the cooperative effect – albeit with far less dramatic shifts in *Z*-selectivity.

Also included in Table 2 are some results from reactions of an ester-stabilised ylide (**20**), two of which have been reported in a previous publication.[22] This ylide reacts with each of benzaldehyde (**2a**) and 2-methylbenzaldehyde (**2f**) in THF at 20 °C with, again, very high *E*-selectivity (see Table 2 entries 5 & 6) while its reactions with *ortho*-heteroatom substituted benzaldehydes, are somewhat more *Z*-selective (Table 2 entries 7 & 8), again clearly demonstrating the operation of the *ortho*-heteroatom effect. The absence of the effect from the reaction of 2-methylbenzaldehyde (Table 2 entry 6) indicates that the operation of the effect, as in our previous study,[7] is dependent the *ortho*-substituent of the aldehyde bearing a lone pair of electrons.

3. Discussion

It has previously been established that reactions of ester-stabilised methyldiphenylphosphonium ylides are under kinetic control.[7,16] Although irreversibility of OPA formation has not been explicitly demonstrated in reactions of keto-stabilised ylides, it seems reasonable by analogy to assume that the reactions detailed here are irreversible, especially in light of the increased *Z*-selectivities observed here, which occurred in THF solvent where high *E*-selectivity is the norm.[2,4] Since the *ortho*-heteroatom effect observed in our previous study is also present in reactions of 2-oxoalkylidenemethyldiphenylphosphoranes, and since the *ortho*-heteroatom-induced increase in *Z*-selectivity is augmented by greater steric bulk at carbon-3 of the ylide oxoalkylidene moiety (cooperative effect), we conclude that the anomalous *Z*-selectivity in these reactions is a consequence of the existence of a *cis*-selective TS (shown in Fig. 1(b) above) similar to that proposed by us previously.

In the proposed TS, the new factor is a bonding interaction between the phosphorus and the *ortho*-heteroatom, causing the TS to be of sufficiently low energy that it can become competitive with the normally favoured *trans*-selective cycloaddition TS. The crowded environment about phosphorus in the proposed TS, results in a significant reorganisation of the phosphorus-substituents in comparison with other Wittig TSs. The position of the aldehyde aryl group is dictated by the phosphorus-heteroatom bond, and, as a result, 1-3 steric interactions (between the aryl group and the ylide phosphorus substituents, Fig. 1(b)) are relatively unimportant in this TS. However, there is a concomitant increase in the potential for 2-3 steric interactions, which are minimized if the ylide α-carbon substituent occupies a pseudo-apical position in the forming ring. Furthermore, such a TS would benefit from the favourable anti-parallel orientation of the dipoles along the aldehyde C–O and ylide C–C(O) bonds, respectively, as is proposed to occur in *E*-selective reactions of stabilised ylides.[10] As a result of the above factors, this TS is *cis*-selective.

The increased *Z*-selectivity in reactions of *ortho*-heteroatom substituted benzaldehydes with ylides that have greater steric bulk at carbon-3 of the oxoalkylidene moiety (cooperative effect) can be rationalised using the same TS arguments. Thus the increased 2-3 interactions that would be engendered by the larger substituent on the ylide α-carbon result in a greater bias towards the *cis*-selective TS since it is better able to accommodate steric bulk in this position. That the cooperative effect exists in reactions of keto-stabilised ylides but not in reactions of ester-stabilised ylides is consistent with our initial working hypothesis: that the alkyl group of the ester moiety in ester-stabilised ylides is too far removed from the ylide α-carbon for its steric bulk to have a bearing on the shape of the TS, while for keto-stabilised ylides the closer proximity of the variable alkyl group to the ylide α-carbon means that differences in this group result in different stereoselectivity in the cycloaddition step.

The existence of the proposed TS is also consistent with selectivity being dependent on the through-space phosphorus-heteroatom bond, and thus essentially *independent* of the electrophilicity of the carbonyl group – i.e. the effect is not a result of through-bond electronic effects exerted by the *ortho*-heteroatom.

In the reactions of β-heteroatom substituted aldehydes that we have studied, the steric effects of the phosphorus substituents, and the influence of these effects on the observed diastereoselectivity, are consistent across all ylide types, including keto-stabilised ylides. We had previously noted[7] that the magnitude of the shift in selectivity for *Z*-alkene or *cis*-OPA in reactions of β-heteroatom substituted aldehydes (compared with analogous unsubstituted aldehydes) decreases in line with the steric bulk of the phosphonium moiety. In the context of our proposed TS model, it is easy to envisage how sterically bulky substituents on phosphorus would reduce the efficacy of phosphorus–heteroatom bonding. In reactions of non-stabilised ylides, the magnitude of this shift decreases in the order Phdibenzophosphole > Ph_3P > $EtPh_2P$; for semi-stabilised ylides the trend is Phdibenzophosphole ≈ $MePh_2P$ > Ph_3P; and for both ester-stabilised and keto-stabilised ylides we are now in a position to conclude that the trend is $MePh_2P$ > Ph_3P. The consistency and generality of these results supports the existence of the proposed TS.

4. Conclusion

Reactions of keto-stabilised ylides and triphenylphosphine-derived ester-stabilised ylides with *ortho*-heteroatom substituted benzaldehydes show an anomalous increase in *Z*-selectivity compared with the reactions of the same ylides with benzaldehyde itself or with 2-methylbenzaldehyde. These results are entirely consistent with those previously observed in reactions of non-stabilised, semi-stabilised and ester-stabilised ylides with β-heteroatom substituted ylides,[7] although the magnitudes of the shifts towards *Z*-selectivity are not as great in the present study. Most significantly, we have demonstrated that the cooperative effect that operates in reactions of benzylides with *ortho*-heteroatom substituted benzaldehydes[7] is replicated in reactions of keto-stabilised ylides with the same aldehydes. We conclude that these reactions are irreversible, and all occur through a similar *cis*-selective [2+2] cycloaddition transition state in which a bond exists between the phosphorus and the β-heteroatom substituent on the aldehyde. The consistency of the results further strengthens the argument that *all* Li salt-free Wittig reactions occur by the [2+2] cycloaddition mechanism proposed by Vedejs and co-workers,[8,9,16] and modified for reactions of stabilised ylides by Aggarwal, Harvey and co-workers.[10]

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18. For further details of the experimental evidence that has been amassed in support of the [2+2] cycloaddition mechanism (including our own contribution to this body of evidence), as well as details of historical significance to its development, we refer the interested reader to reference 7.
19. As an aside, we note that betaines are not involved in the mechanism of the Li-salt free Wittig but, if generated through a non-Wittig route, will collapse to OPA and hence give phosphine oxide and alkene as shown as Scheme 2.
20. As a further aside, we also note that almost all Li-salt free Wittig reactions are under kinetic control. As also shown in Scheme 2, a very small number of reactions of non-stabilised ylides are known in which the formation of *cis*-OPA is reversible, resulting in enhanced production of *trans*-OPA (and hence *E*-alkene) relative to the initial amount formed of this intermediate. Most of these involve ethylides and benzaldehydes - see reference 7 for a full discussion of the phenomenon and an exhaustive list of the examples for which it is known to operate.
21. Reaction vessels and NMR tubes were protected from light where possible by being wrapped in aluminium foil. NMR samples of the crude reaction mixtures were obtained as soon as the work-up of the reaction was complete.
22. Byrne P. A.; Rajendran, K. V.; Muldoon, J.; Gilheany, D. G. *Org. Biomol. Chem.* **2012**, *10*, 3531.

Supplementary Data

A Supplementary Data document is available containing details of experimental procedures, assignments of alkene Z/E ratios, and full characterization of all new phosphonium salts and alkenes.